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DOCUMENT-IDENTIFIER: US 20030096013 A1
TITLE: Preparation of submicron sized particles with polymorph control

Summary of Invention Paragraph (4):
[0004] Another approach is disclosed in U.S. Pat. No. 5,118,528 which discloses a process for preparing nanoparticles. The process includes the steps of: (1) preparing a liquid phase of a substance in a solvent or a mixture of solvents to which may be added one or more surfactants; (2) preparing a second liquid phase of a non-solvent or a mixture of non-solvents, the non-solvent is miscible with the solvent or mixture of solvents for the substance; (3) adding together the solutions of (1) and (2) with stirring; and (4) removing of unwanted solvents to produce a colloidal suspension of nanoparticles. The '528 Patent discloses that it produces particles of the substance smaller than 500 nm without the supply of energy. In particular the '528 Patent states that it is undesirable to use high energy equipment such as sonicators and homogenizers.

Summary of Invention Paragraph (12):
[0012] One approach is directed to the production of suspended particles coated with protein. U.S. Pat. No. 5,916,596, issued to Desai et al., discloses the application of high shear to a mixture of an organic phase having a pharmacologically active agent dispersed therein and an aqueous medium containing a biocompatible polymer. The mixture is sheared in a high pressure homogenizer at a pressure in the range of from about 3,000 to 30,000 psi. The '596 patent provides that the mixture must contain substantially no surfactants because the combined use of a surfactant with a protein results in the formation of large, needle-like crystalline particles that increase in size during storage. See columns 17-18, example 4. Example 2 discloses that crude emulsion may be sonicated to produce nanoparticles ranging from 350-420 nanometers.

Summary of Invention Paragraph (15):
[0015] Another approach to preparing a water-insoluble drug for in vivo delivery centers on reducing the size of the particles that deliver the drug. In one such series of patents, which include U.S. Pat. Nos. 6,228,399; 6,086,376; 5,922,355; and 5,660,858, Parikh et al. discloses that sonication may be used to prepare microparticles of the water-insoluble compound. Of these patents, U.S. Pat. No. 5,922,355 discloses an improvement to a method that uses sonication for making the smaller particles. The improvement comprises mixing an active pharmacological agent with a phospholipid and surfactants in a single-phase aqueous system and applying energy to the system to produce the smaller particles.

Summary of Invention Paragraph (18):
[0018] Microprecipitation by pH shifting is another technology used to prepare dispersions of a nanoparticulate pharmaceutical agent. See, e.g., U.S. Pat. Nos. 5,665,331 and 5,662,883. This technology involves dissolving a pharmaceutical agent in an aqueous base which is then neutralized to form a dispersion.

Summary of Invention Paragraph (19):
[0019] In yet another approach, such as that disclosed in U.S. Pat. No. 5,766,635, issued to Spenlenhauer et al., nanoparticles have been prepared by dissolving a poly(ethylene) oxide and/or poly(propylene) oxide in an organic solvent, mixing the organic solution so formed with an aqueous solution to cause nanoparticles to precipitate out of solution, and microfluidizing the precipitated solution without

the use of surfactants.

Detail Description Paragraph (22):
[0064] Suitable solvent anti-solvent precipitation technique is disclosed in U.S. Pat. Nos. 5,118,528 and 5,100,591 which are incorporated herein by reference and made a part hereof. The process includes the steps of: (1) preparing a liquid phase of a biologically active substance in a solvent or a mixture of solvents to which may be added one or more surfactants; (2) preparing a second liquid phase of a non-solvent or a mixture of non-solvents, the non-solvent is miscible with the solvent or mixture of solvents for the substance; (3) adding together the solutions of (1) and (2) with stirring; and (4) removing of unwanted solvents to produce a colloidal suspension of nanoparticles. The '528 Patent discloses that it produces particles of the substance smaller than 500 nm without the supply of energy.

Detail Description Paragraph (27):
[0069] pH Shift Precipitation

Detail Description Paragraph (28):
[0070] pH shift precipitation techniques typically include a step of dissolving a drug in a solution having a pH where the drug is soluble, followed by the step of changing the pH to a point where the drug is no longer soluble. The pH can be acidic or basic, depending on the particular pharmaceutical compound. The solution is then neutralized to form a presuspension of submicron sized particles of the pharmaceutcially active compound. One suitable pH shifting precipitation process is disclosed in U.S. Pat. No. 5,665,331, which is incorporated herein by reference and made a part hereof. The process includes the step of dissolving of the pharmaceutical agent together with a crystal growth modifier (CGM) in an alkaline solution and then neutralizing the solution with an acid in the presence of suitable surface-modifying surface-active agent or agents to form a fine particle dispersion of the pharmaceutical agent. The precipitation step can be followed by steps of diafiltration clean-up of the dispersion and then adjusting the concentration of the dispersion to a desired level. This process of reportedly leads to microcrystalline particles of Z-average diameters smaller than 400 nm as measured by photon correlation spectroscopy.

Detail Description Paragraph (30):
[0072] Other examples of pH shifting precipitation methods are disclosed in U.S. Pat. Nos. 5,716,642; 5,662,883; 5,560,932; and 4,608,278, which are incorporated herein by reference and are made a part hereof.

Detail Description Paragraph (50):
[0092] The seed compound can be precipitated from a drug containing solution of any of the above-described processes. This method includes the steps of adding the pharmaceutically-active compound in sufficient quantity to exceed the solubility of the pharmaceutically-active compound in the first solution to create a supersaturated solution. The supersaturated solution is treated to precipitate the pharmaceutically-active compound in the desired polymorphic form. Treating the supersaturated solution includes aging the solution for a time period until the formation of a crystal or crystals is observed to create a seeding mixture. Treating the solution also includes subjecting the solution to temperature shifting or pH shifting. It is also possible to add energy to the supersaturated solution to cause the pharmaceutically-active compound to precipitate out of the solution in the desired polymorph. The energy can be added in a variety of ways including the energy addition steps described above. Further energy can be added by heating or exposing the presuspension to electromagnetic energy, particle beam or electron beam sources. The electromagnetic energy includes using a laser beam, dynamic electromagnetic energy, or other radiation sources It is further contemplated utilizing ultrasound, static electric field and a static magnetic field as the energy addition source.

Detail Description Paragraph (55):
[0097] The drug solution or the presuspension or both the drug solution and the presuspension may be provided with one or more optional surface active compounds such as an anionic surfactant, a cationic surfactant, a nonionic surfactant or a biological surface active molecule added thereto. Suitable anionic surfactants include but are not limited to potassium laurate, sodium lauryl sulfate, sodium

dodecylsulfate, alkyl polyoxyethylene sulfates, sodium alginate, dioctyl sodium sulfosuccinate, phosphatidyl choline, phosphatidyl glycerol, phosphatidyl inosine, phosphatidylserine, phosphatidic acid and their salts, glyceryl esters, sodium carboxymethylcellulose, cholic acid and other bile acids (e.g., cholic acid, deoxycholic acid, glycocholic acid, taurocholic acid, glycodeoxycholic acid) and salts thereof (e.g., sodium deoxycholate, etc.). Suitable cationic surfactants include but are not limited to quaternary ammonium compounds, such as benzalkonium chloride, cetyltrimethylammonium bromide, lauryldimethylbenzylammonium chloride, acyl camitine hydrochlorides, or alkyl pyridinium halides. As anionic surfactants, phospholipids may be used. Suitable phospholipids include, for example phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidylglycerol, phosphatidic acid, lysophospholipids, egg or soybean phospholipid or a combination thereof. The phospholipid may be salted or desalted, hydrogenated or partially hydrogenated or natural semisynthetic or synthetic.

Detail Description Paragraph (56):
[0098] Suitable nonionic surfactants include: polyoxyethylene fatty alcohol ethers (Macrogol and Brij), polyoxyethylene sorbitan fatty acid esters (Polysorbates), polyoxyethylene fatty acid esters (Myrj), sorbitan esters (Span), glycerol monostearate, polyethylene glycols, polypropylene glycols, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, aryl alkyl polyether alcohols, polyoxyethylene-polyoxypropylene copolymers (poloxomers), polaxamines, methylcellulose, hydroxycellulose, hydroxy propylcellulose, hydroxy propylmethylcellulose, noncrystalline cellulose, polysaccharides including starch and starch derivatives such as hydroxyethylstarch (HES), polyvinyl alcohol, and polyvinylpyrrolidone. In a preferred form of the invention, the nonionic. surfactant is a polyoxyethylene and polyoxypropylene copolymer and preferably a block copolymer of propylene glycol and ethylene glycol. Such polymers are sold under the tradename POLOXAMER also sometimes referred to as PLURONIC.RTM., and sold by several suppliers including Spectrum Chemical and Ruger. Among polyoxyethylene fatty acid esters is included those having short alkyl chains. One example of such a surfactant is SOLUTOL.RTM. HS 15, polyethylene-660-hydroxystearate, manufactured by BASF Aktiengesellschaft.

Detail Description Paragraph (58):
[0100] It may also be desirable to add a pH adjusting agent to the second solution such as sodium hydroxide, hydrochloric acid, tris buffer or citrate, acetate, lactate, meglumine, or the like. The second solution should have a pH within the range of from about 3 to about 11.

Detail Description Paragraph (64):
[0103] To a 3-L flask add 1680 mL of Water for Injection, heat liquid to 60.degree. C.-65.degree. C., and then slowly add 44 grams of Pluronic F-68 (poloxamer 188), and 12 grams of sodium deoxycholate, stirring after each addition to dissolve the solids. After addition of solids is complete, stir for another 15 minutes at 60.degree. C.-65.degree. C. to ensure complete dissolution. Prepare a 50 mM tris (tromethamine) buffer by dissolving 6.06 grams of tris in 800 mL of Water for Injection. Titrate this solution to pH 8.0 with 0.1 M hydrochloric acid. Dilute the resulting solution to 1 liter with additional Water for Injection. Add 200 mL of the tris buffer to the poloxamer/deoxycholate solution. Stir thoroughly to mix solutions.

Detail Description Paragraph (74):
[0111] To a 500-mL stainless steel vessel add 252 mL of Water for Injection. Heat liquid to 60-65.degree. C., and then slowly add 6.6 grams of Pluronic F-68 (poloxamer 188), and 0.9 grams of sodium deoxycholate, stirring after each addition to dissolve the solids. After addition of solids is complete, stir for another 15 minutes at 60-65.degree. C. to ensure complete dissolution. Prepare a 50 mM tris (tromethamine) buffer by dissolving 6.06 grams of tris in 800 mL of Water for Injection. Titrate this solution to pH 8.0 with 0.1 M hydrochloric acid. Dilute the resulting solution to 1 liter with additional Water for Injection. Add 30 mL of the tris buffer to the poloxamer/deoxycholate solution. Stir thoroughly to mix solutions.

Detail Description Paragraph (76):
[0113] Charge a syringe pump with 18-mL of itraconazole solution prepared in a previous step. Position a mechanical stirrer into the surfactant solution so that the blades are fully immersed. Cool the container to 0.degree. C.-5.degree. C. by immersion in an ice bath. Using the syringe pump, slowly (1-3 mL/min) add all of the itraconazole solution to the stirred, cooled surfactant solution. A stirring rate of at least 700 rpm is recommended. Immerse an ultrasonicator horn in the resulting suspension so that the probe is approximately 1 cm above the bottom of the stainless steel vessel. Sonicate (10,000 to 25,000 Hz, at least 400W) for 15 to 20 minute in 5-minute intervals. After the first 5-minute sonication, remove the ice bath and proceed with further sonication. At the end of ultrasonication, the temperature of the suspension in the vessel does not exceed 75.degree. C.

Detail Description Paragraph (80):
[0115] Prepare a 50 mM tris (tromethamine) buffer by dissolving 6.06 grams of tris in 800 mL of Water for Injection. Titrate this solution to pH 8.0 with 0.1 M hydrochloric acid. Dilute the resulting solution to 1 liter with additional Water for Injection. To a 3-L flask add 1680 mL of Water for Injection. Add 200 mL of the tris buffer to the 1680 mL of water. Stir thoroughly to mix solutions.

Detail Description Paragraph (86):
[0119] To a 500-mL flask add 252 mL of Water for Injection. Prepare a 50 mM tris (tromethamine) buffer by dissolving 6.06 grams of tris in 800 mL of Water for Injection. Titrate this solution to pH 8.0 with 0.1 M hydrochloric acid. Dilute the resulting solution to 1 liter with additional Water for Injection. Add 30 mL of the tris buffer to the water. Stir thoroughly to mix solutions.

Detail Description Paragraph (128):
[0150] The precipitated suspension was pH adjusted to 7.5-8.5 using sodium hydroxide and hydrochloric acid then homogenized (Avestin C-50 piston-gap homogenizer) for 10 passes at 10,000 psi. The NMP was removed by performing 2 successive centrifugation steps replacing the supernatant each time with a fresh surfactant solution, which contained the desired concentrations of surfactants needed to stabilize the suspension (see Table 1). The suspension was homogenized for another 10 passes at 10,000 psi. The final suspension contained particles with a mean particle size of less than 1 .mu.m, and 99% of particles less than 2 .mu.m. FIG. 8 is a photomicrograph of the final prednisolone suspension after homogenization.

Detail Description Paragraph (129):
[0151] A variety of different surfactants at varying concentrations were used in the centrifugation/surfactant replacement step (see Table 1). Table 1 lists combinations of surfactants that were stable with respect to particle size (mean <1 .mu.m, 99%<2 .mu.m), pH (6-8), drug concentration (less than 2% loss) and re-suspendability (resuspended in 60 seconds or less).

Detail Description Paragraph (133):
[0153] 32 g of prednisolone was dissolved into 40 mL of NMP. Gentle heating at 40-50.degree. C. was required to effect dissolution. The drug NMP concentrate was subsequently dripped at 2.5 mL/min into 2 liters of a stirred solution that consisted of 0.1.2% lecithin and 2.2% glycerin. No other surface modifiers were added. The surfactant system was buffered at pH=8.0 with 5 mM tris buffer and the temperature was held at 0.degree. C. to 5.degree. C. during the entire precipitation process. The post-precipitated dispersion was next homogenized cold (5-15.degree. C.) for 20 passes at 10,000 psi. Following homogenization, the NMP was removed by centrifuging the suspension, removing the supernatant, and replacing the supernatant with fresh surfactant solution. This post-centrifuged suspension was then rehomogenized cold (5.degree. C.-15.degree. C.) for another 20 passes at 10,000 psi. The particles produced by this process had a mean diameter of 0.927 .mu.m with 99% of the particles being less than 2.36 .mu.m.

Detail Description Paragraph (136):
[0154] Surfactant (2.2 g of poloxamer 188) was dissolved in 6 mL of N-methyl-2-pyrrolidinone. This solution was stirred at 45.degree. C. for 15 minutes, after which 1.0 g of nabumetone was added. The drug dissolved rapidly. Diluent was prepared which consisted of 5 mM tris buffer with 2.2% glycerol, and adjusted to pH

8. A 100-mL portion of diluent was cooled in an ice bath. The drug concentrate was slowly added (approximately 0.8 mL/min) to the diluent with vigorous stirring. This crude suspension was homogenized at 15,000 psi for 30 minutes and then at 20,000 psi for 30 minutes (temperature=5.degree. C.). The final nanosuspension was found to be 930 nm in effective mean diameter (analyzed by laser diffraction). 99% of the particles were less than approximately 2.6 microns.

Detail Description Paragraph (139):
[0155] Nabumetone (0.987 grams) was dissolved in 8 mL of N-methyl-2-pyrrolidinone. To this solution was added 2.2 grams of Solutol.RTM.. HS 15. This mixture was stirred until complete dissolution of the surfactant in the drug concentrate. Diluent was prepared, which consisted of 5 mM tris buffer with 2.2% glycerol, and which was adjusted to pH 8. The diluent was cooled in an ice bath, and the drug concentrate was slowly added (approximately 0.5 mL/min) to the diluent with vigorous stirring. This crude suspension was homogenized for 20 minutes at 15,000 psi, and for 30 minutes at 20,000 psi.

Detail Description Paragraph (143):
[0157] Itraconazole concentrate was prepared by dissolving 10.02 grams of itraconazole in 60 mL of N-methyl-2-pyrrolidinone. Heating to 70.degree. C. was required to dissolve the drug. The solution was then cooled to room temperature. A portion of 50 mM tris(hydroxymethyl)aminomethane buffer (tris buffer) was prepared and was pH adjusted to 8.0 with 5M hydrochloric acid. An aqueous surfactant solution was prepared by combining 22 g/L poloxamer 407, 3.0 g/L egg phosphatides, 22 g/L glycerol, and 3.0 g/L sodium cholate dihydrate. 900 mL of the surfactant solution was mixed with 100 mL of the tris buffer to provide 1000 mL of aqueous diluent.

CLAIMS:

10. The method of claim 9, wherein the step of precipitating the compound is accomplished by a process selected from the group consisting of: microprecipitation, emulsion precipitation, solvent anti-solvent precipitation, phase inversion precipitation, pH shift precipitation, infusion precipitation, temperature shift precipitation, solvent evaporation precipitation, reaction precipitation, and compressed fluid precipitation.

22. The method of claim 5, wherein the diluent has a first pH wherein the pharmaceutical compound has a first solubility such that the compound is dissolved in the diluent and wherein the step of precipitating comprises the step of changing the pH of the diluent to a second pH wherein the compound has a second solubility lower than the first solubility and the compound precipitates from the diluent.

54. The method of claim 53, wherein the step of treating the supersaturated solution comprises the step of a process selected from the group of aging the supersaturated solution, temperature shifting the solution and pH shifting of the solution.

76. The method of claim 36, wherein the step of precipitating is by changing the pH of the first solvent.

98. The method of claim 97, wherein the step of treating the supersaturated solution comprises the step selected from the group consisting of aging the supersaturated solution, temperature shifting the solution or pH shifting the solution.